Actualización en el tratamiento de la macroglobulinemia de Waldenström y de sus complicaciones

Dra Eugenia Abella. Hospital del Mar, Barcelona

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Conflicto de intereses- Eugenia Abella

- He proporcionado asesoramiento científico a Janssen, Celgene, GSK, Beigene, Sanofi
- He participado en reuniones médicas organizades por Janssen, BMS Celgene, GSK, Beigene, Sanofi
- He recibido pagos por presentaciones y asesoría de Janssen, BMS Celgene , GSK, Beigene, Sanofi
- He recibido honorarios por esta presentación

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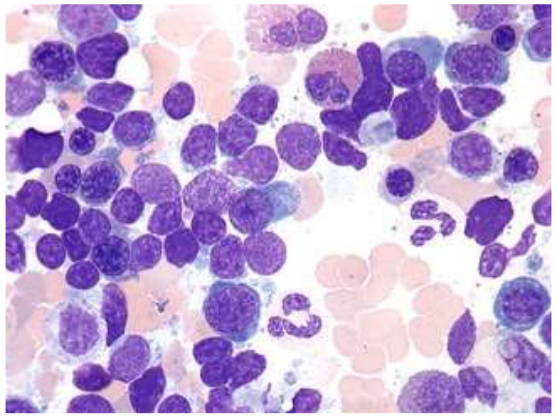
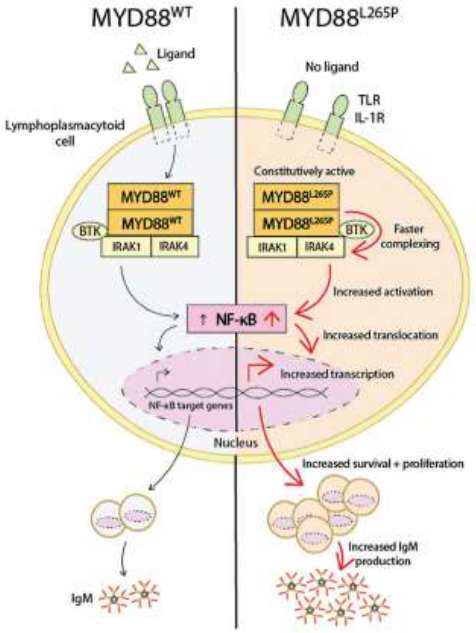
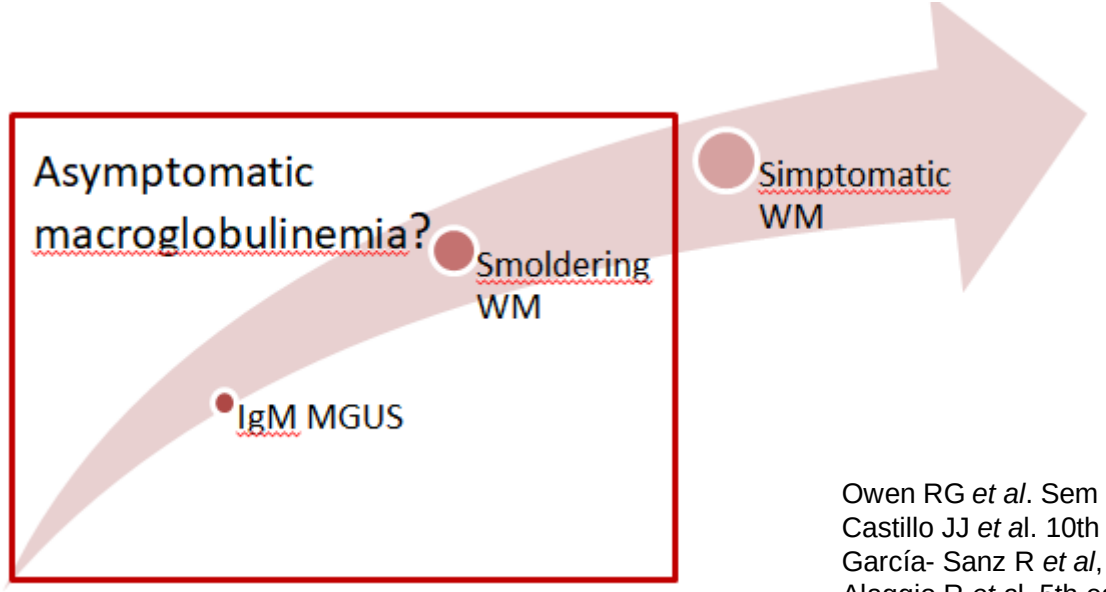
Introduction

Lymphoplasmacytic lymphoma associated with a monoclonal IgM

- *MYD88* ^{L265P} gene mutation 97% (rt- pcr)
- *CXCR4* gene mutations 30% . (NGS).Shorter treatment free survival
- Del 6q have clinical features associated with adverse prognosis and therefore high risk IPSSWM
- TERT mut have an inferior response to BTK inhibitors?







. By tumor mass
. By monoclonal protein

Owen RG *et al*. Sem Oncol 2003; 30: 110-115
Castillo JJ *et al*. 10th IWWM. Lancet Haemetol, 2020
García- Sanz R *et al*, Br J Haematol, 2020
Alaggio R *et al*. 5th ed WHO . Leukemia 2022; 36

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Definition of IgM-related phenomenon in macroglobulinemia

	IgM Monoclonal Component	Symptoms of Tumor Mass/ Infiltration (Adenopathy Anemia)	Marrow Infiltration > 10%	IgM-Mediated Symptoms
MGUS	+	−	−	−
Smoldering macroglobulinemia	+	−	+	−
IgM-related disorder (eg, cold agglutinin hemolytic anemia, type II cryoglobulin, neuropathy, amyloidosis)	+	−	±	+
Macroglobulinemia	+	+	+	±

Abbreviations: IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; +, positive; −, negative; ±, equivocal.

Even with low levels of IgM and minimal clonal marrow infiltration some patients require therapy for IgM-related disorders

Adapted from Gertz M. Am J Hematol 2023; 98

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Impact of CXCR4 mutations in clinical features of patients with Waldenström Macroglobulinemia

	CXCR4 mutated	CXCR4 wild type
Serum IgM level	+++	+
Risk of hyperviscosity	+++	+
Lymphadenopathy	+	+++
Splenomegaly	+	+
Serum beta-2-microglobulin level	+	++
Thrombocytopenia	++	+
Leukopenia	+	+
Anemia	+	+
Bone marrow involvement	++	+
Acquired von Willebrand disease	+++	+
Time to therapy initiation	Shorter	Longer

CXCR4 mut/ BTK inhibitors

- Longer time to response
- Lower rates of major or VGPR
- Shorter PFS

- not associated with worse or better OS

Detecting CXCR4 mutations has not been standardized.

Castillo JJ *et al*, Exp Rew hematol 2019

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Indications for treatment initiation

CLINICAL CRITERIA	LABORATORY CRITERIA
Systemic symptoms (recurrent fever, night sweats, weight loss, **fatigue**)	Symptomatic cryoglobulinemia
Hyperviscosity (viscosity > 4 cP)	Cold agglutinin anemia
Symptomatic or bulky (≥ 5 cm in maximum diameter)	Immune hemolytic and/or thrombocytopenia
Symptomatic hepatomegaly and or splenomegaly	Nephropaty related to WM
Symptomatic organomegaly and/or organ or tissue infiltration (CNS)	Amyloidosis related to WM
Peripheral neuropathy Immune-mediated neuronal damage by antibodies to myelin-associated glycoprotein (MAG)	Hb ≤ 10 g/dL Platelet count < 100 x 10^9/L Clonal IgM > 60 g/L???

•Few patients get RC despite new treatments

Leblond V *et al*, 8th IWWM ,Blood,2016; 128
Simon L *et al*, Br J Haematol, 2018
Kapoor P *et al,* JAMA Oncol, 2017
Abeykoon JP *et al*. Am J hematol.2018;93

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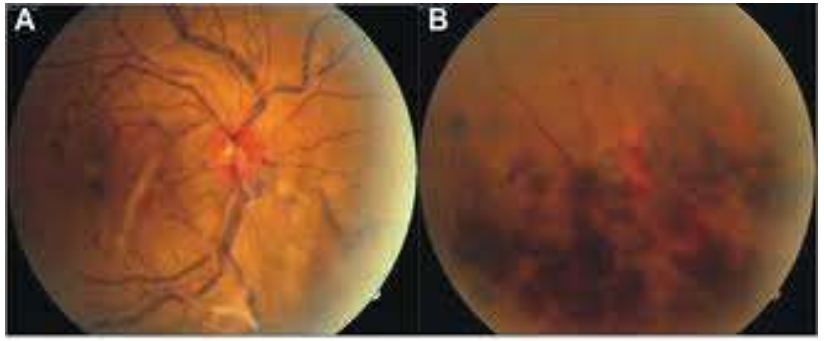

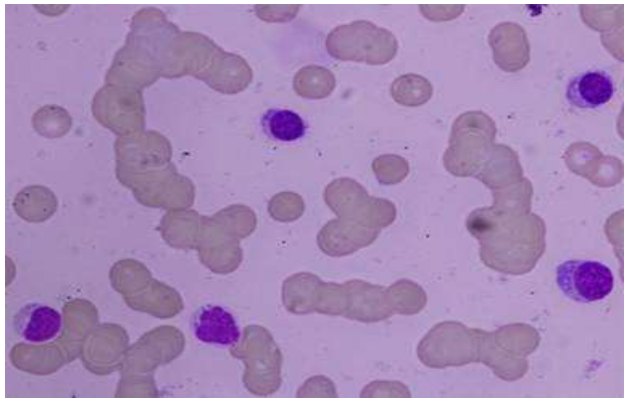

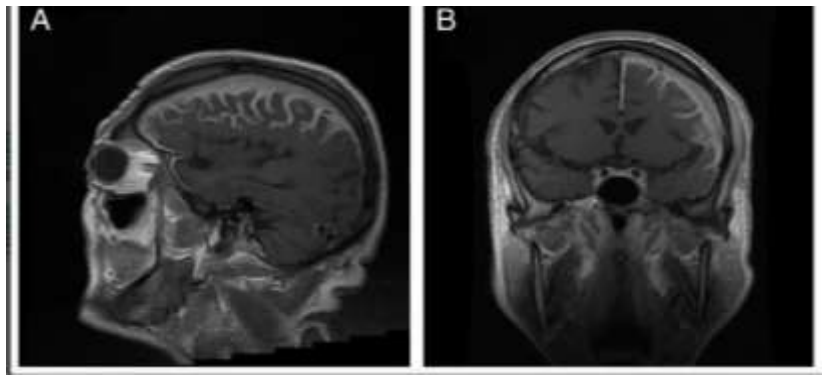

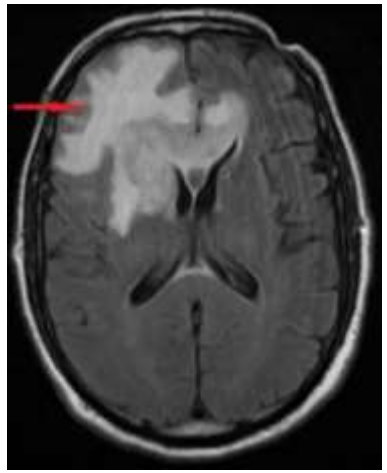

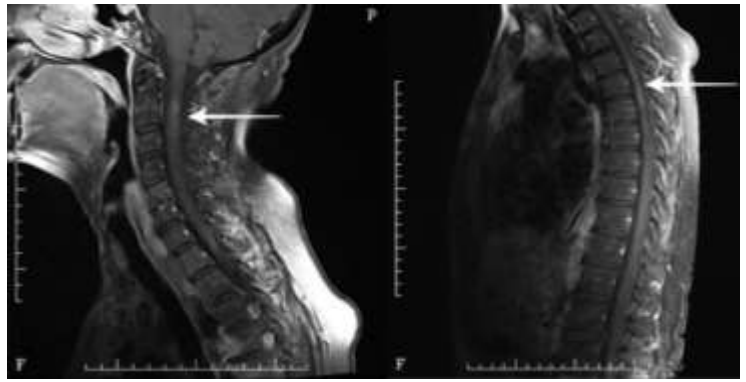

Minnema MC et al. Haematologica 2017; 102

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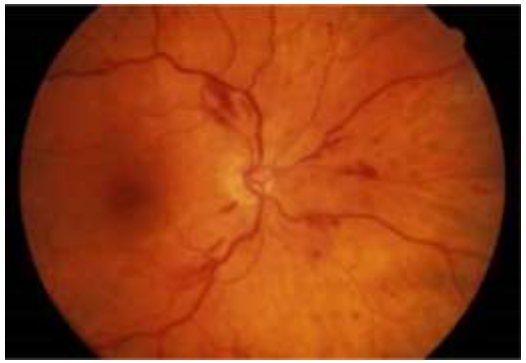
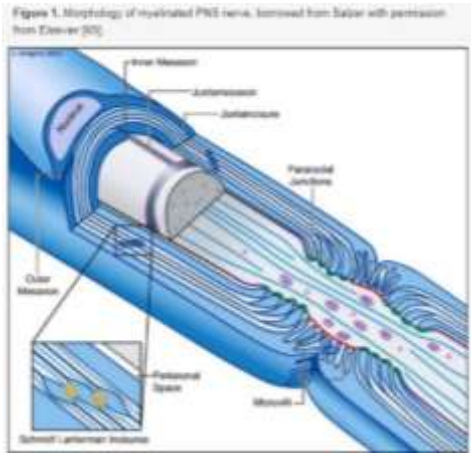
Neurological symptoms

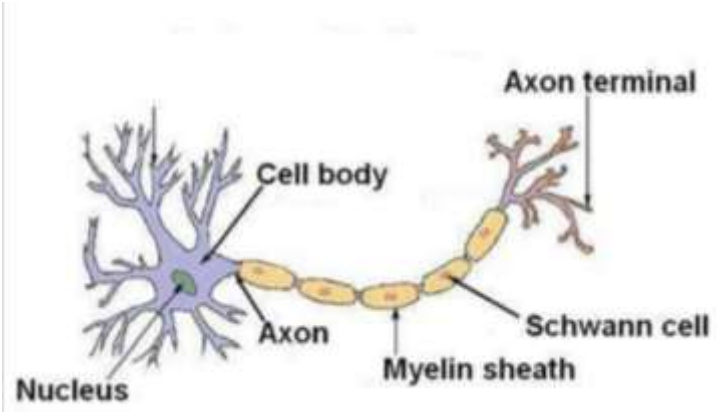
1- Caused by the accumulation of IgM : **Hyperviscosity syndrome**

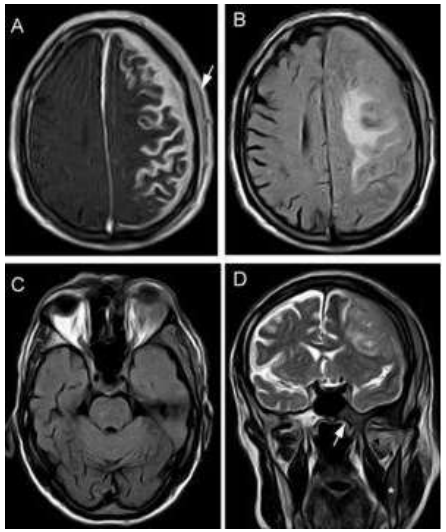
2- **IgM- related neuropathies**

3- Caused to organ infiltration : **Bing Neel syndrome**









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1- Hyperviscosity Syndrome

Plasma : H_20, variable M weight proteins

Centipoises or miliPascal.second
mPas.s=1 cP

Cn 1,4-1,8 cP a 37ºC
Hyperviscosity ≥ 4 cP

IgM > 50-60 g/L
Incidence : 13%

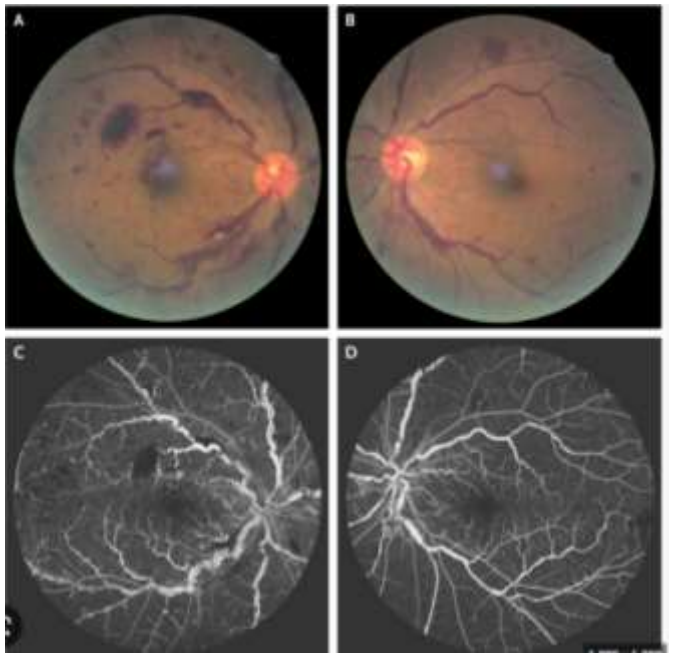
↑ Blood or serum Viscosity → hypoxemia

↓

Neurological disorders

Visual disturbances

Bleeding



Rogers AP et al, 2022
Brysland SA et al. Thromb Haemost 2022; 122
Gertz MA. Blood, 2018;132

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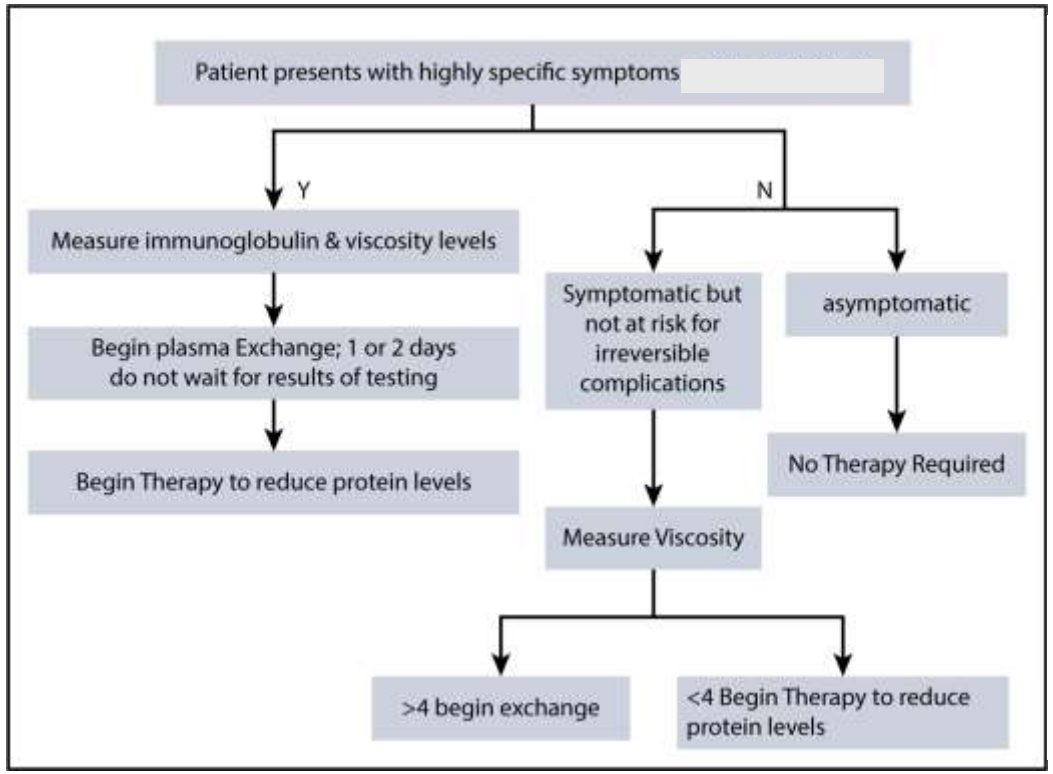
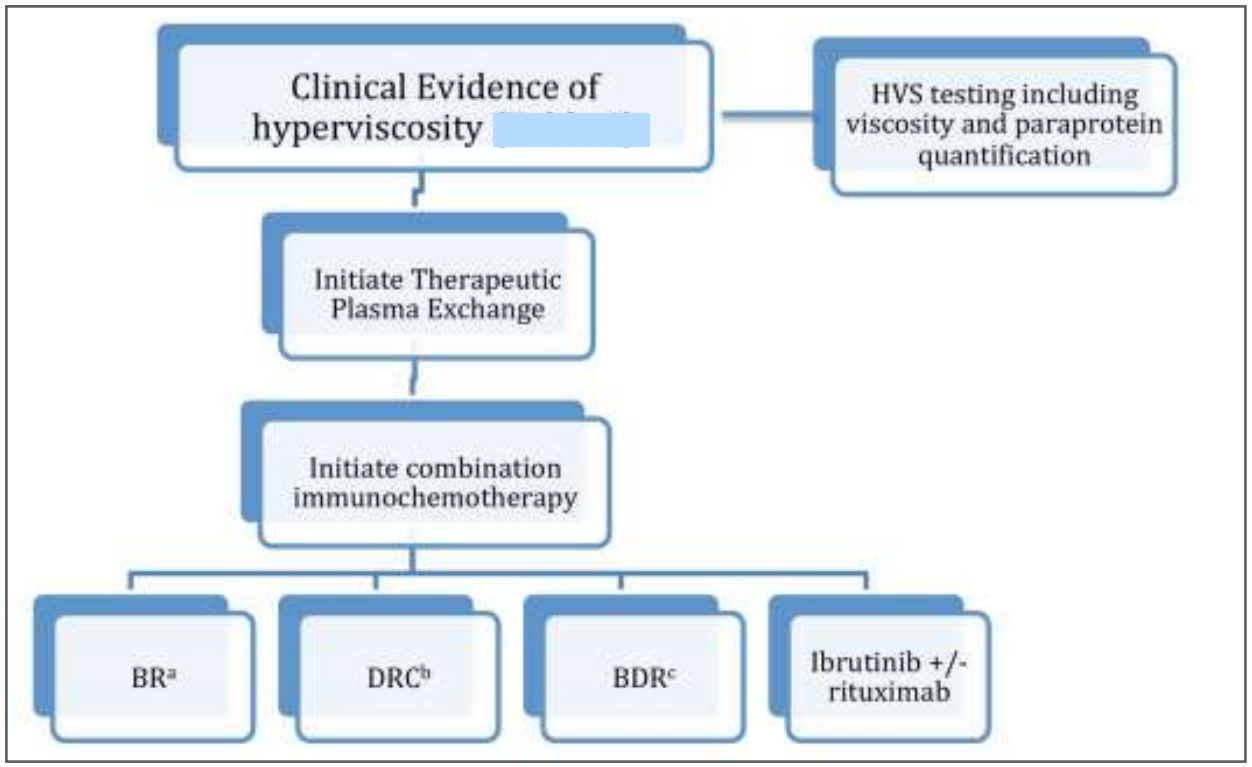
Therapeutic algorithm for hyperviscosity





Gertz MA. Blood, 2018;132
Weaver A et al, Front Oncol, 2020;10;815

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2- IgM-related peripheral neuropathies (PN)

- Immune-mediated neuronal damage by antibodies to myelin-associated glycoprotein (MAG)
- Non anti-MAG PN [anti ganglioside (GM1, GM2, GD1b, GD3, GT1b, GQ1b) anti sulfatide]
- AL (deposits of AL within various parts of the nerve)
- Cryoglobulins (vasculitis/ischemic damage)

PN incidence 15-30% of MGUS and WM cases
it's a slow progressive neuropathy, but after about 10 or 15 years,
about 50% of the patients become disabled if not treated.

Latov, N. WM Associate Neuropathy. Lymphoma, Leukemia & Myeloma Congress; October , 2022. NY.
Khwaja J *et al*, Haematologica , 2022;107

Van de Mortel JPM *et al*. Hemato 2022; 3.

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3- Bing Neel Syndrome (1936)

Involvement of the CNS (brain , spinal cord, CSF) (prior, during o after WM diagnosis)

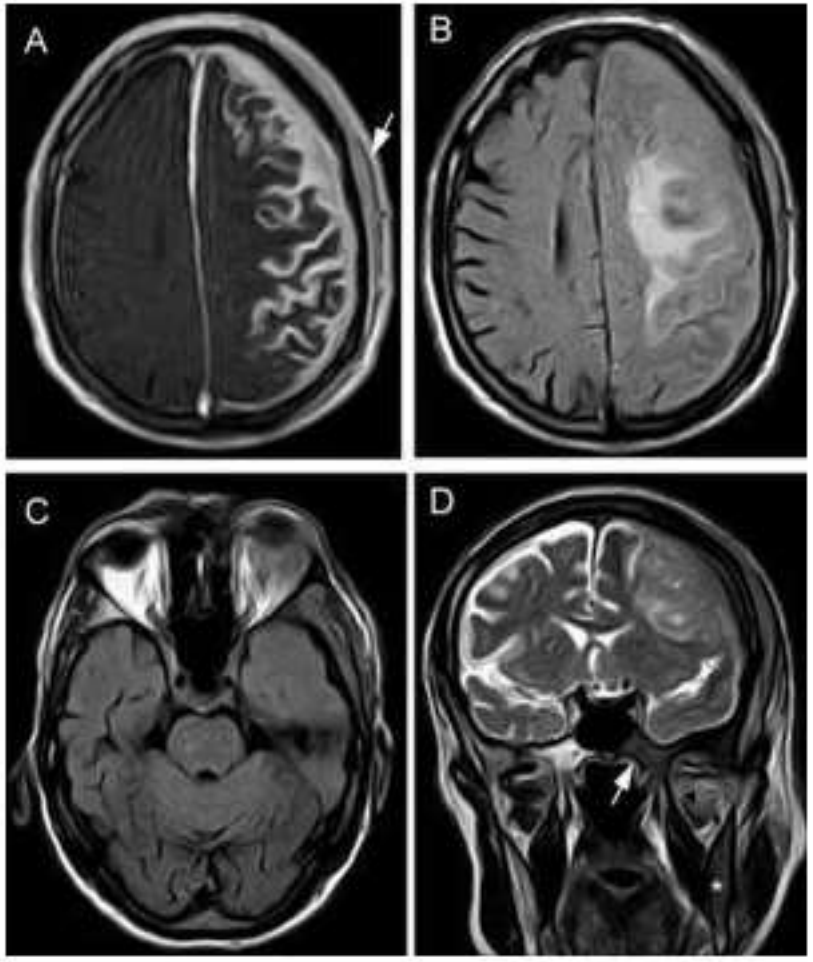
- Incidence : 0,8-1%
- Differential diagnosis :
  - Hyperviscosity syndrome
  - Anti- MAG PN
  - PCNSL
  - Other NHL with involvement CNS

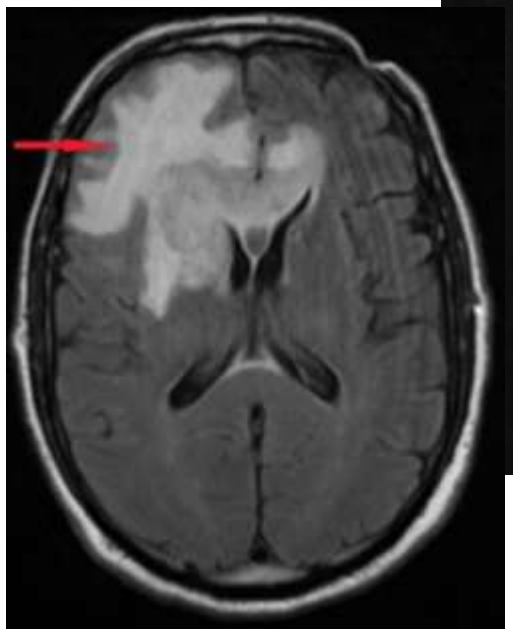
Diagnostic criteria:

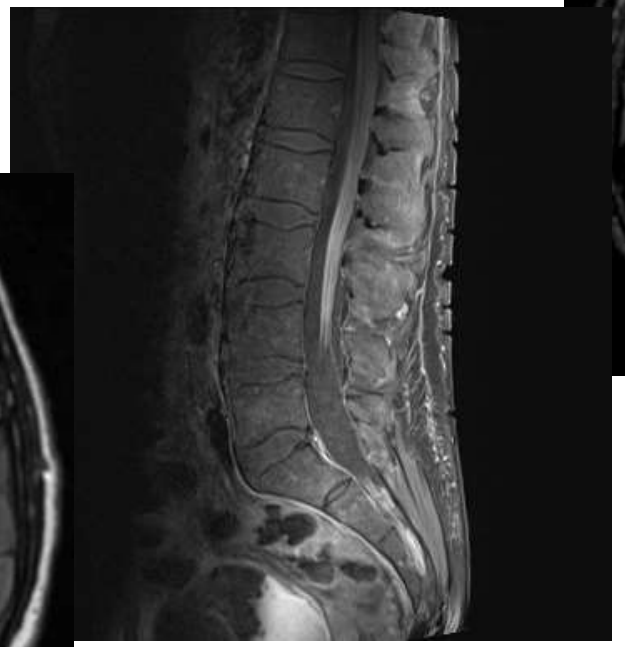
- Histological biopsy of LPL: morphology, Immunochemistry
- Analysis of the CSF :
  - morphology, CMF (B-cell or plasma-cell markers, light chain restriction)
  - Igs gene rearrangement analysis
  - MYD88 ^{mut}
  - CXCR4 ^{mut}
  - PEP Ifix CSF

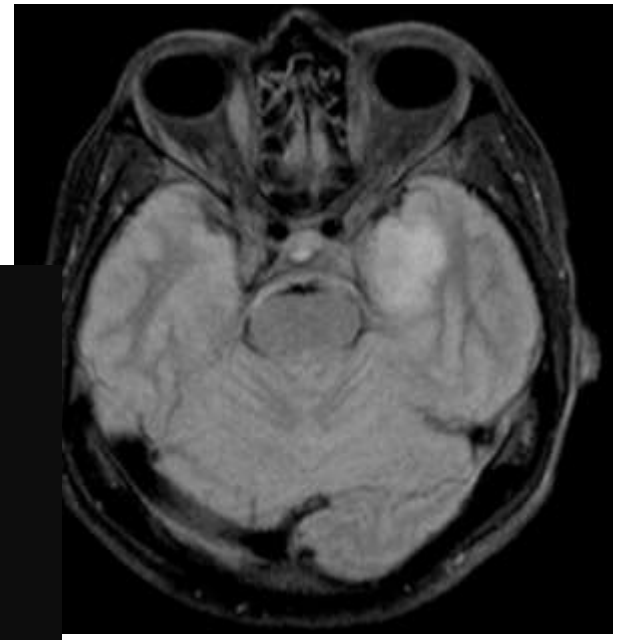
Minnema MC et al. Haematologica 2017; 102 Minnema MC et al. Haematologica 2017; 102

To perform MRI brain and spinal cord









Diffuse form: leptomeningeal lymphoid cell infiltration
Tumoral form: unifocal o multifocal

MRI is supportive but not sufficient for BNS diagnosis
Normal MRI does not exclude BNS (11%)

Minnema MC et al. Haematologica 2017; 102

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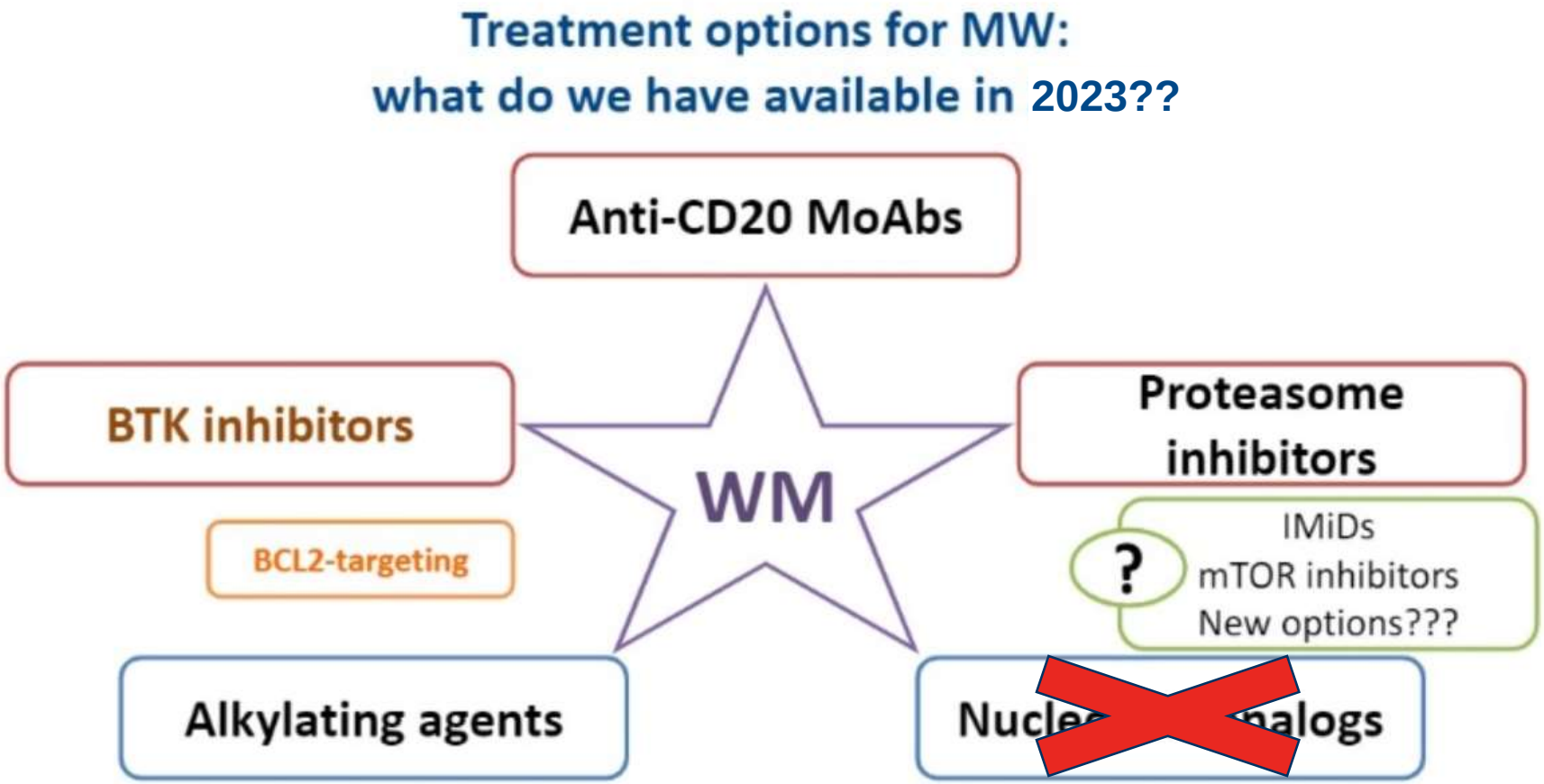
Waldenström Macroglobulinemia treatment



•*CXCR4* mut: “resistance” to Ibrutinib but can also give resistance to bendamustine, fludarabine, bortezomib ?

Adapted from Kastritis E, 17th IMW, 2019

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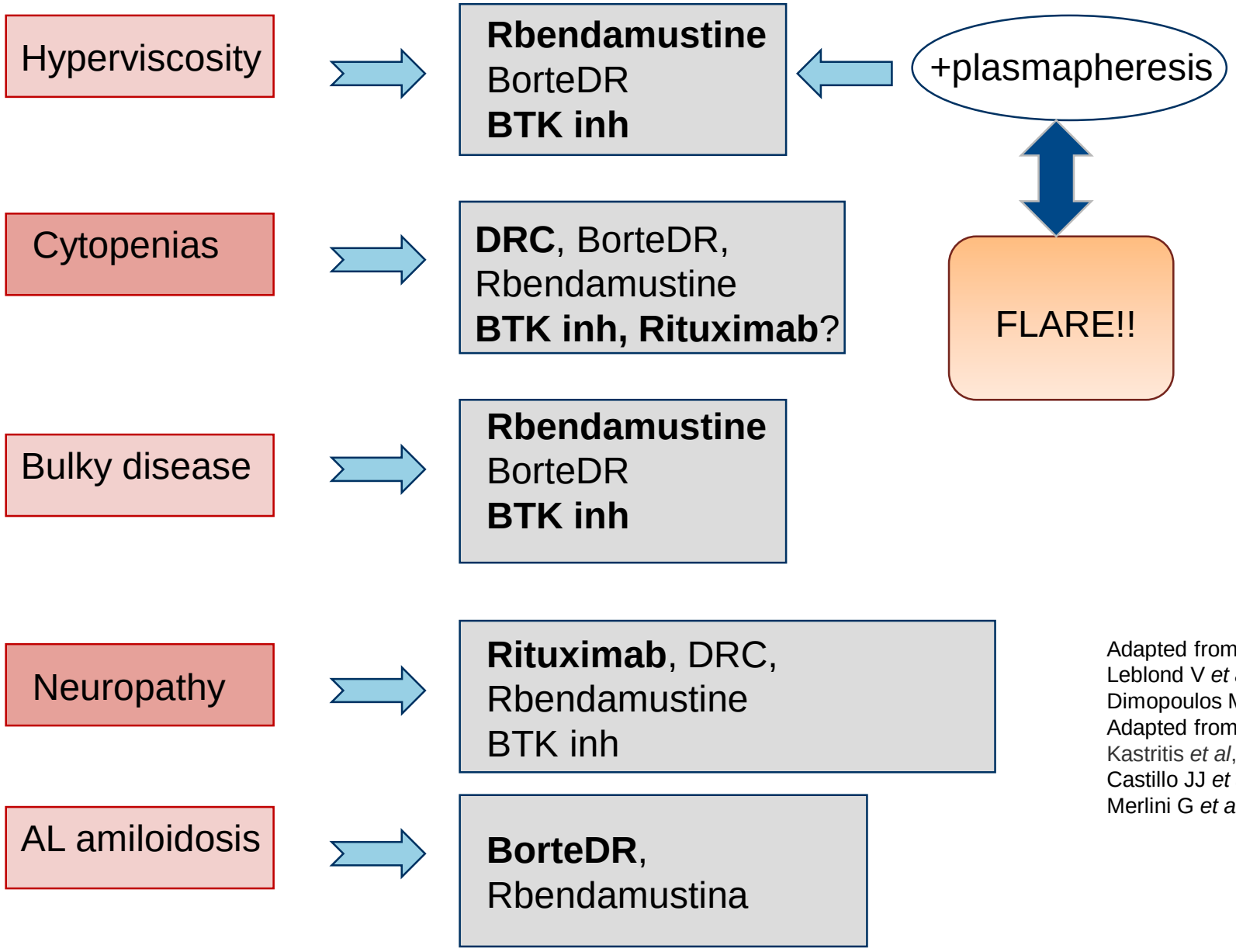
WM treatment adjusted to clinical-laboratory manifestations



Adapted from Kastritis E , EHA 2017
Leblond V *et a*l Blood, 2016;128
Dimopoulos MA, Kastritis E. Blood, 2019
Adapted from Simon L Baron M , Leblond V, Br J Haematol 2018
Kastritis *et al*, Annals of Oncology, 2018;29,
Castillo JJ *et al*. Lancet Haematol 2020; 7: e827–37
Merlini G *et al*. Sem hematol, 2023 (in press)

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Bendamustine and rituximab (BR) versus dexamethasone, rituximab, and cyclophosphamide (DRC) in patients with Waldenström Macroglobulinemia

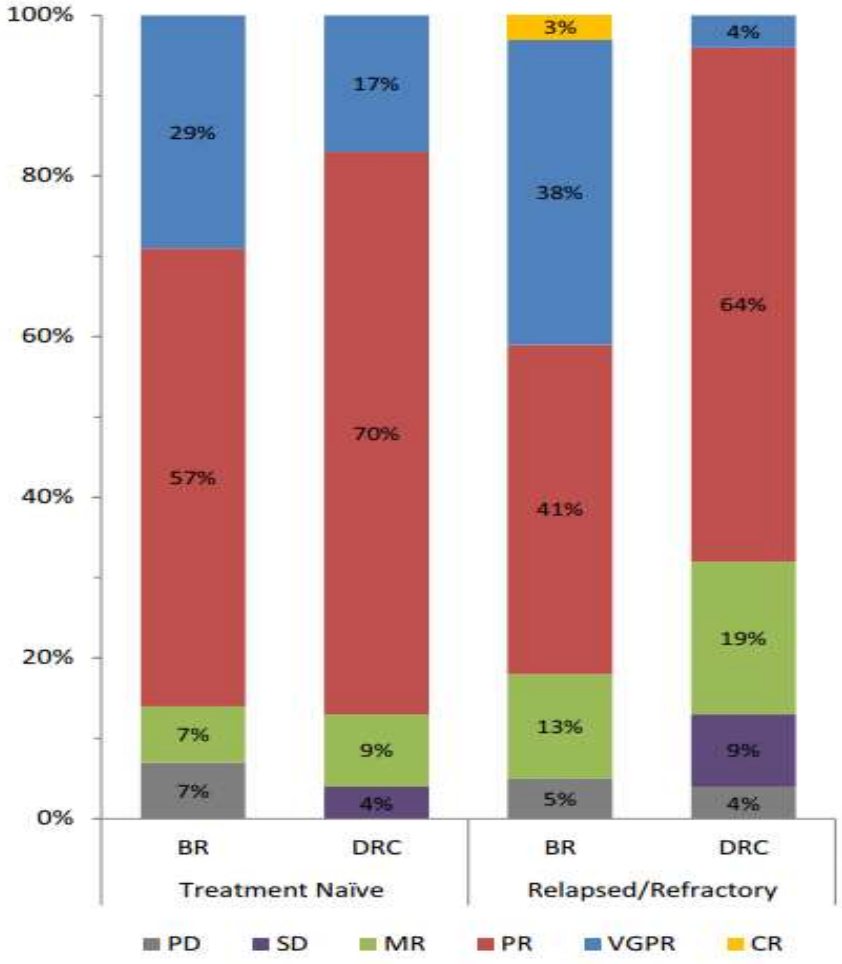
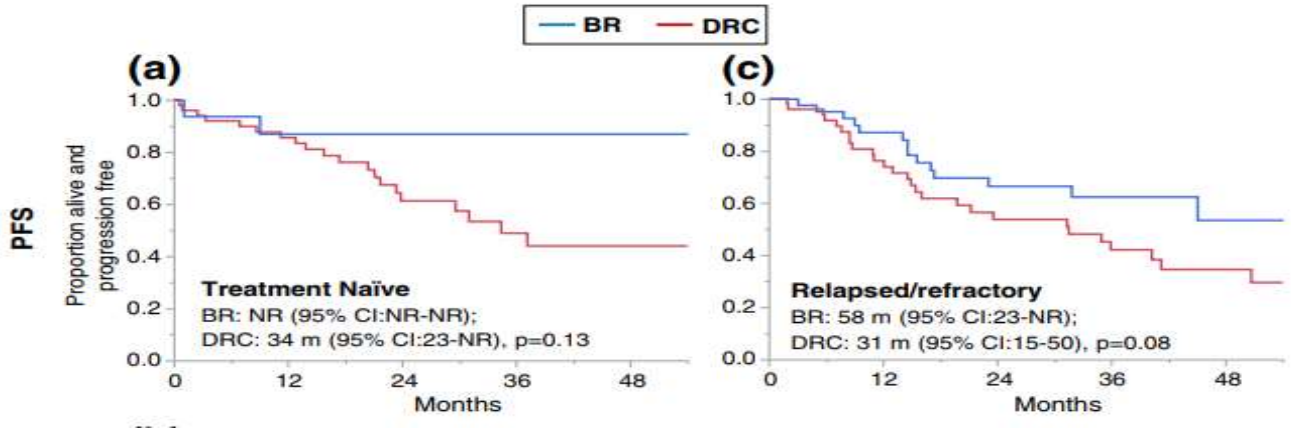


Fig. 1 Best response rates from BR and DRC. CR complete response, VGPR very good partial response, PR partial response, MR minor response, SD stable disease, PD progressive disease



-TN: Benda-R had a better median time to best response (6,1 vs 11 m)

-2-y PFS was improved in Benda-R (88 vs 61%,p=0.07)

- The MYD88 mutation status does not appear to impact the activity of BR or DRC.

- DRC is currently an alternative regimen for first line treatment if disease burden is low

Paludo J *et al*, Br J Haematol, 2017;179. Paludo J *et al,* Ann Hematol, 2018
Grimont ChN *et al*, Acta Haematol .2020

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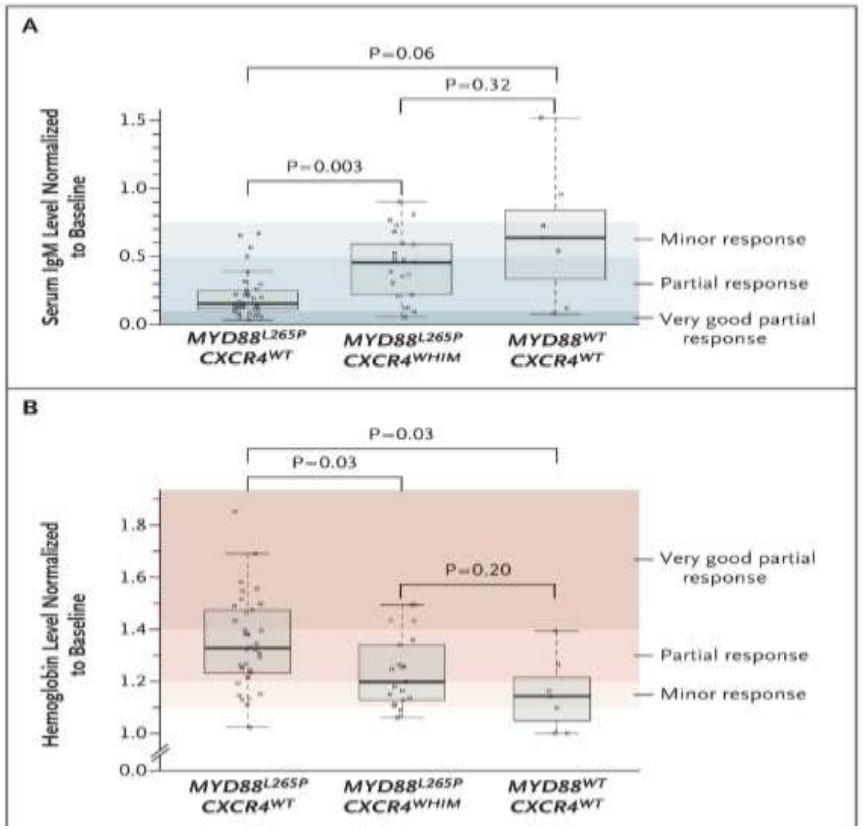
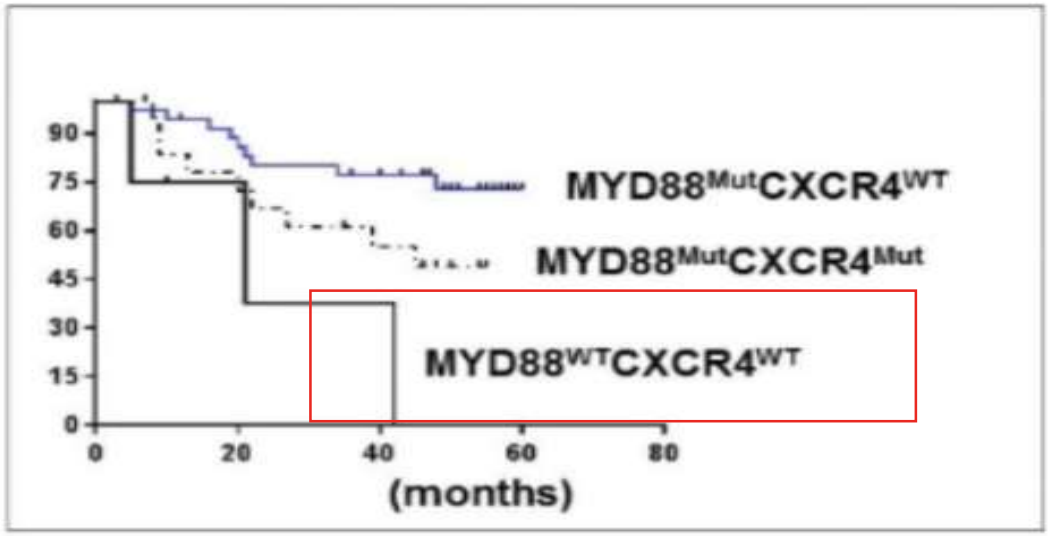
Ibrutinib in previously treated WM . Updated PFS





ORR: 90% Major RR (≥PR): 73%

5 years PFS: 54%
5 years OS: 87%

Response Depth, time to major response , PFS are impacted by *Myd88* and *CXCR4* mutation status

Treon SP et al. N eng J Med,2015; 372
Treon SP *et al*, ICML, 2019
Treon SP *et al*, IMW 2019
Treon S *et al*, JCO, 2020; 39

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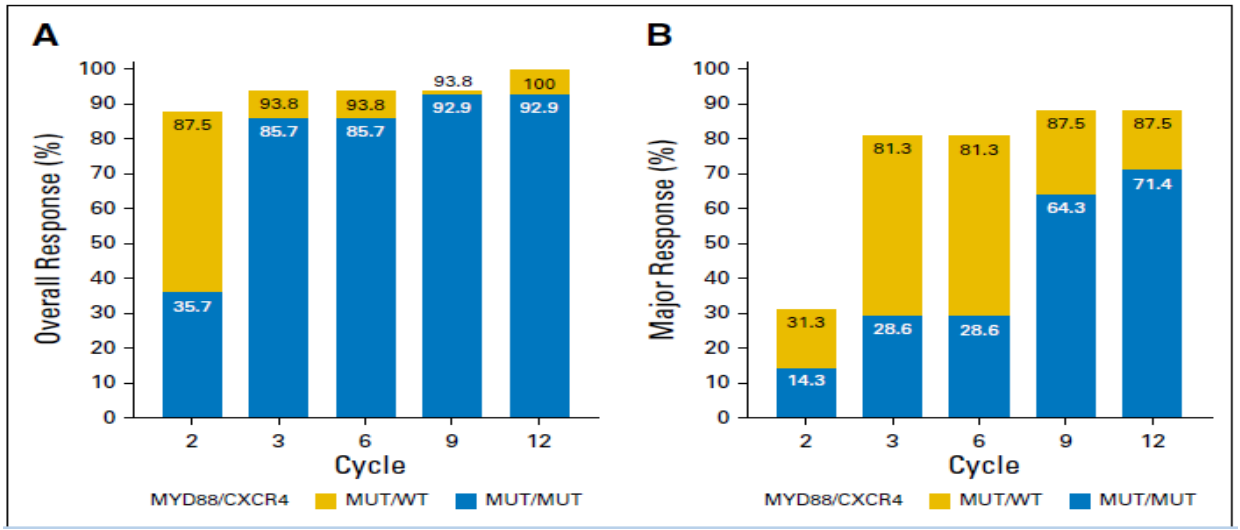
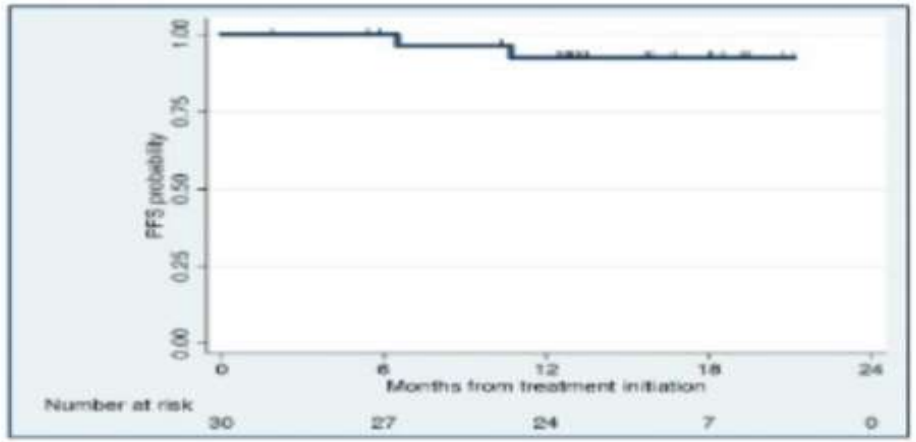
Ibrutinib Monotherapy in Symptomatic, Treatment-Naïve Patients With Waldenström Macroglobulinemia.



	CXCR4^{WT}	*CXCR4*^{mut}	p
MR (%)	94	71	
VGPR (%)	31	7	
TTMR (m)	1,8	7,3	0.01



30 pts, 100% *MYD88* mut, 47% *CXCR4* mut

ORR	100%
Major R	83%
PFS 18 m	92%
OS 18 m	100%

Ibrutinib responses were affected by *CXCR4* mut status.

Treon S *et al*, J Clin Oncol, 2018;36

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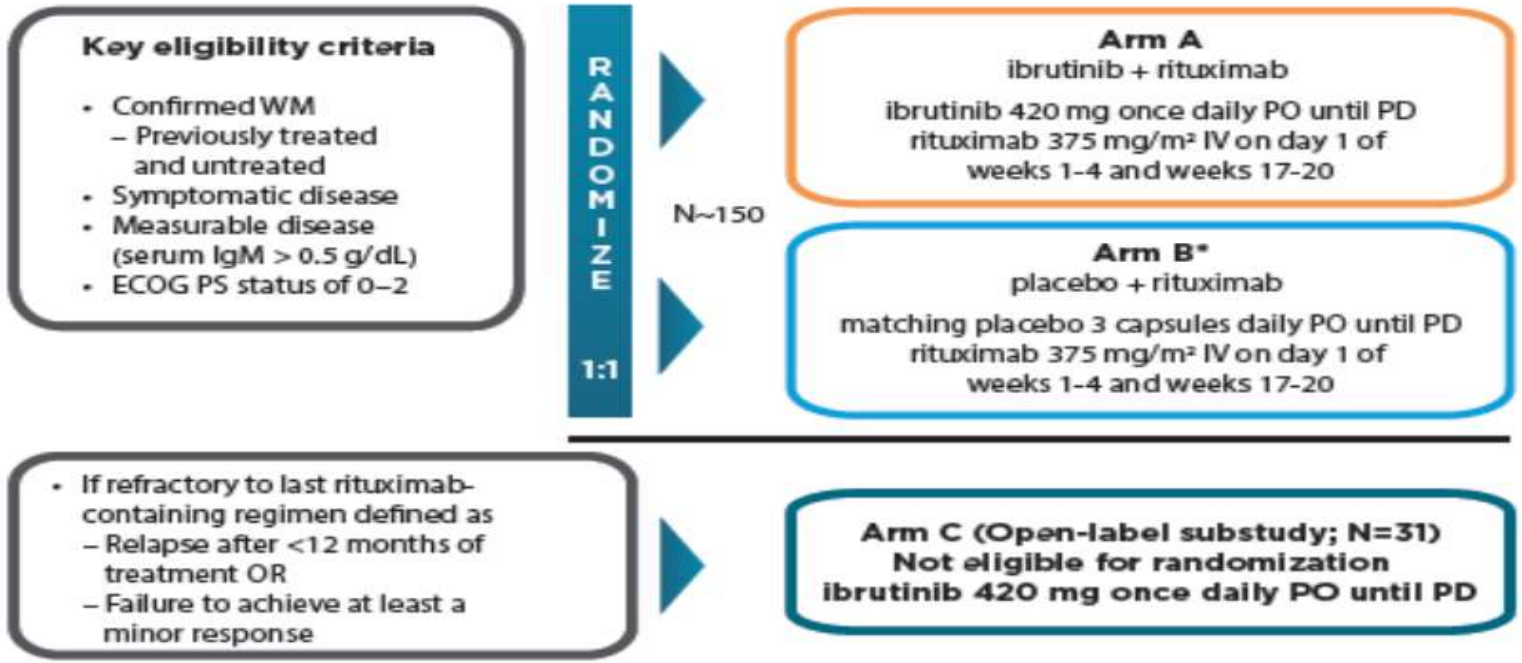
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia

INNOVATE: Ibrutinib-Rituximab vs Placebo -Rituximab . A multicenter open-label phase 3 study



Dimopoulos MA *et al,* N Eng J Med 2018; 378

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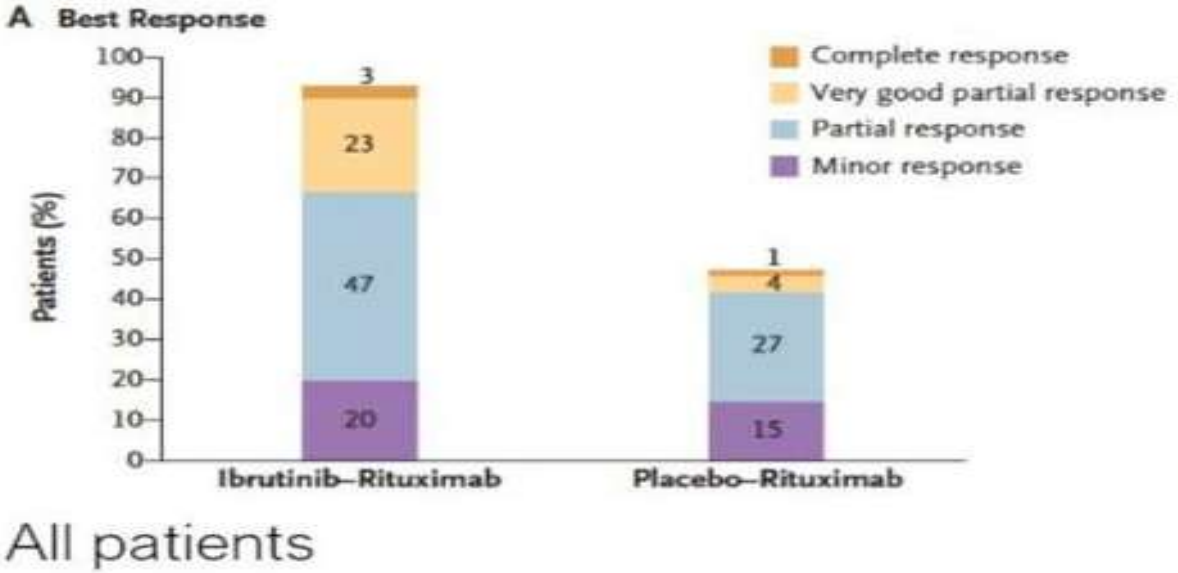
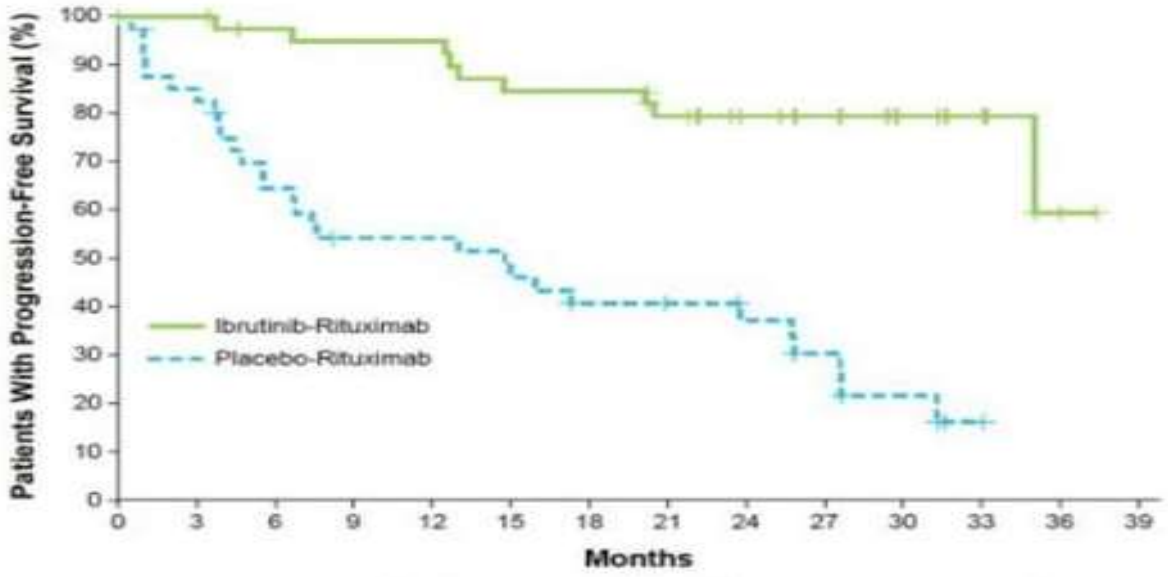
Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia



All patients



Relapsed/refractory patients

30 month PFS rate : 82% vs 28%

improved PFS was seen in treatment-naïve patients, relapsed patients, and independent of MYD88/CXCR4 genotype

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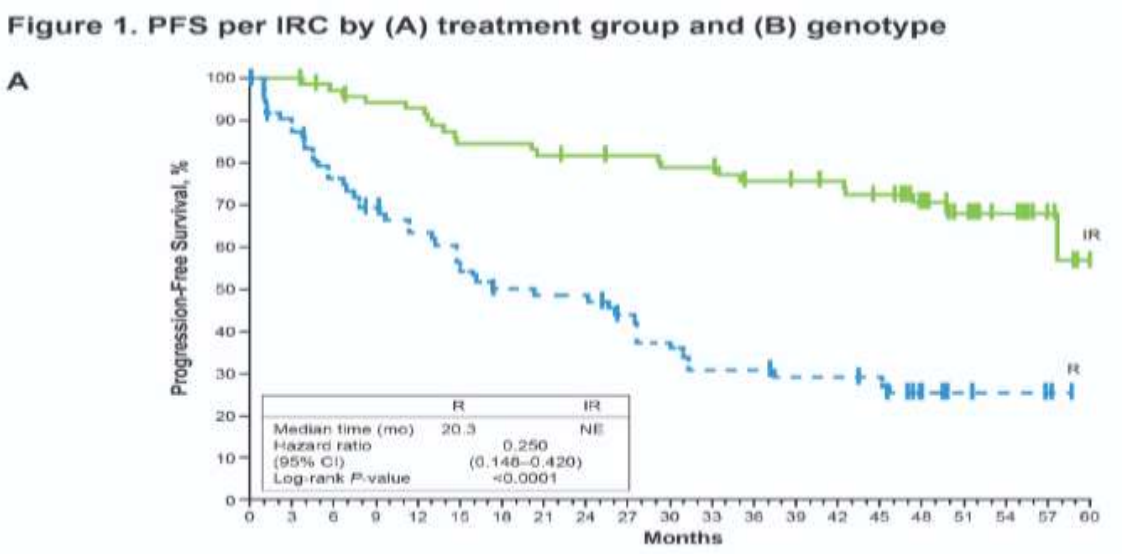
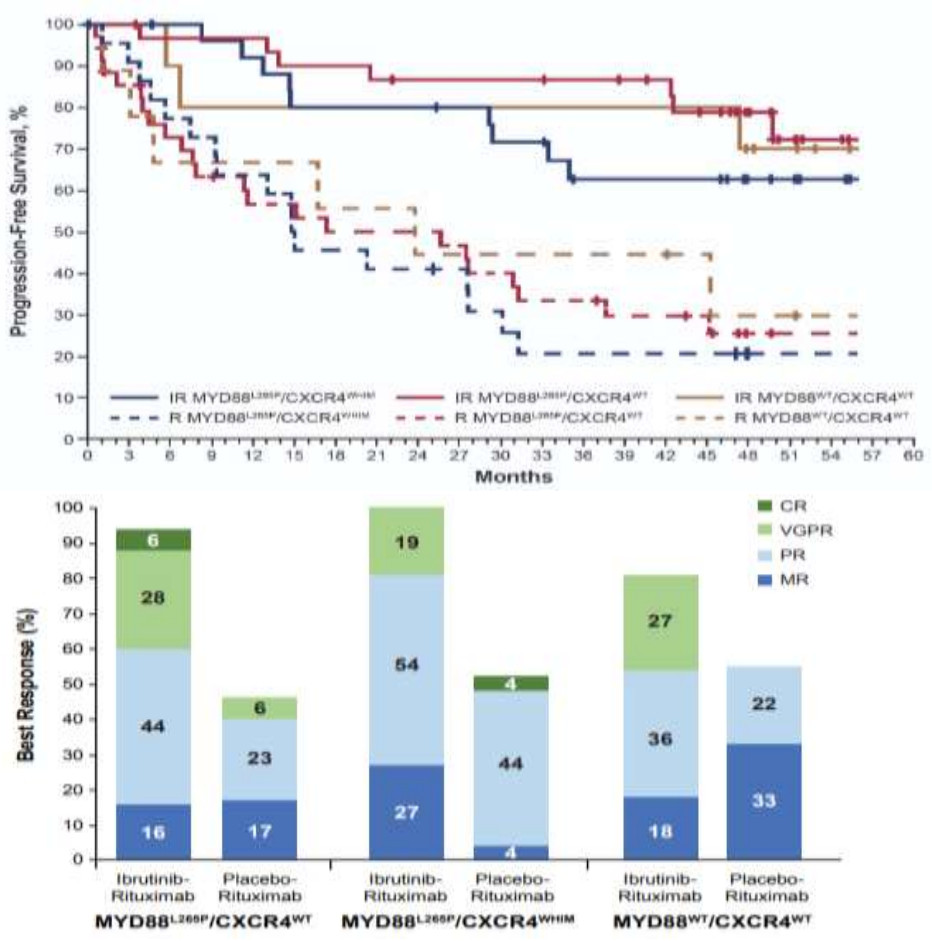
Dimopoulos MA *et al*, N Eng J Med 2018; 378

Five-Year Follow-Up of Ibrutinib Plus Rituximab Vs Placebo Plus Rituximab for Waldenstrom's Macroglobulinemia: Final Analysis From the Randomized Phase 3 iNNOVATE™ Study (5 years)





- I+R shows superiority regardless of genotype, for both TN and previously treated patients with prior treatment
- No data to recommend I+R over Ibrutinib alone

- No use of Ibrutinib alone in *MYD88* WT

Buske Ch et al, JCO, 2021;52

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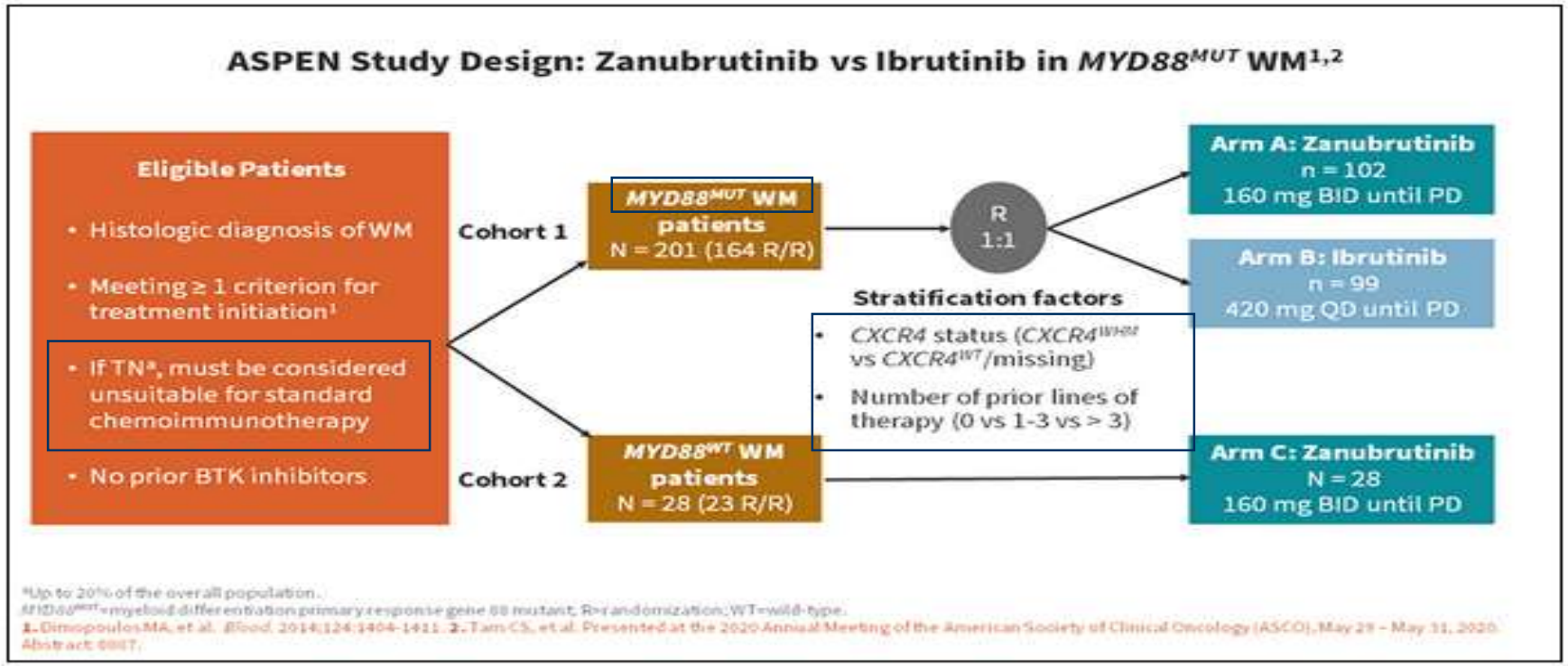
New BTK inhibitors: Zanubrutinib

A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study



Primary end point: proportion of CR and VGPR
Secondary end points: MRR, PFS, DOR , Dis burden , safety
8% and 11% of Ibrut and zanub patients had *a CXCR4 WHIM* mut

Tam CS et al, Blood, 2020;136

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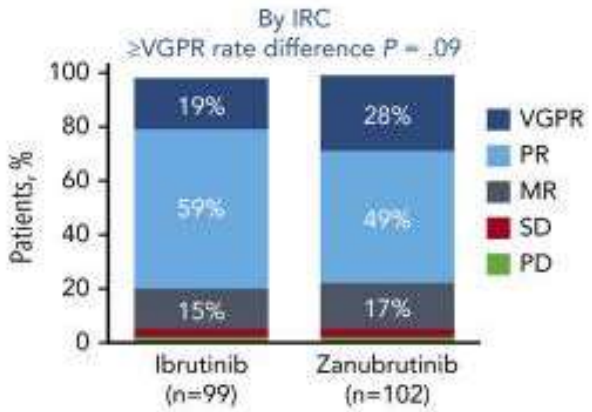
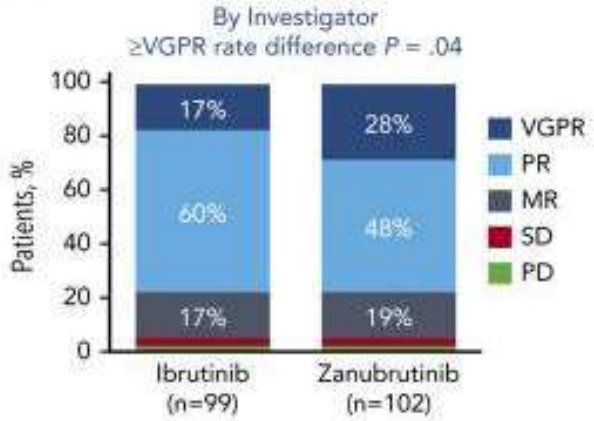
ASPEN: Zanubrutinib vs ibrutinib in patients with *MYD88*^{L265P} Waldenström macroglobulinemia

Best Overall Responses



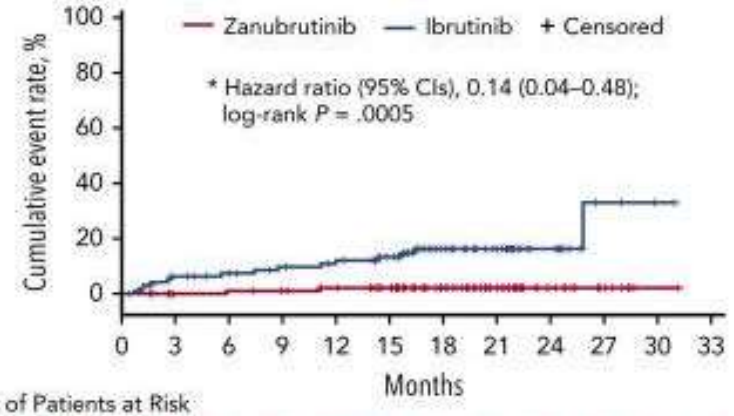


AE Categories, n (%) (Pooled Terms)	All Grades	
	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter*	15 (15.3)	2 (2.0)
Diarrhea (PT)	31 (31.6)	21 (20.8)
Hemorrhage	58 (59.2)	49 (48.5)
Major hemorrhage	9 (9.2)	6 (5.9)
Hypertension	17 (17.3)	11 (10.9)
Neutropenia*	13 (13.3)	30 (29.7)
Infection	66 (67.3)	67 (66.3)

*Descriptive 2-sided $P < .05$

Data cutoff 31Aug2019

Time-to-event analysis of atrial fibrillation/flutter events



No. of Patients at Risk

Zanubrutinib	101	95	94	92	89	81	57	34	15	7	1	0
Ibrutinib	98	87	83	78	74	66	46	28	13	3	1	0

•The incidence and severity of most BTK-associated toxicities (including atrial fibrillation) were lower with zanubrutinib than ibrutinib.

TAM CS *et al*, Blood,2020;136
Dimopoulos MA *et al*, Blood Adv, 2020;4

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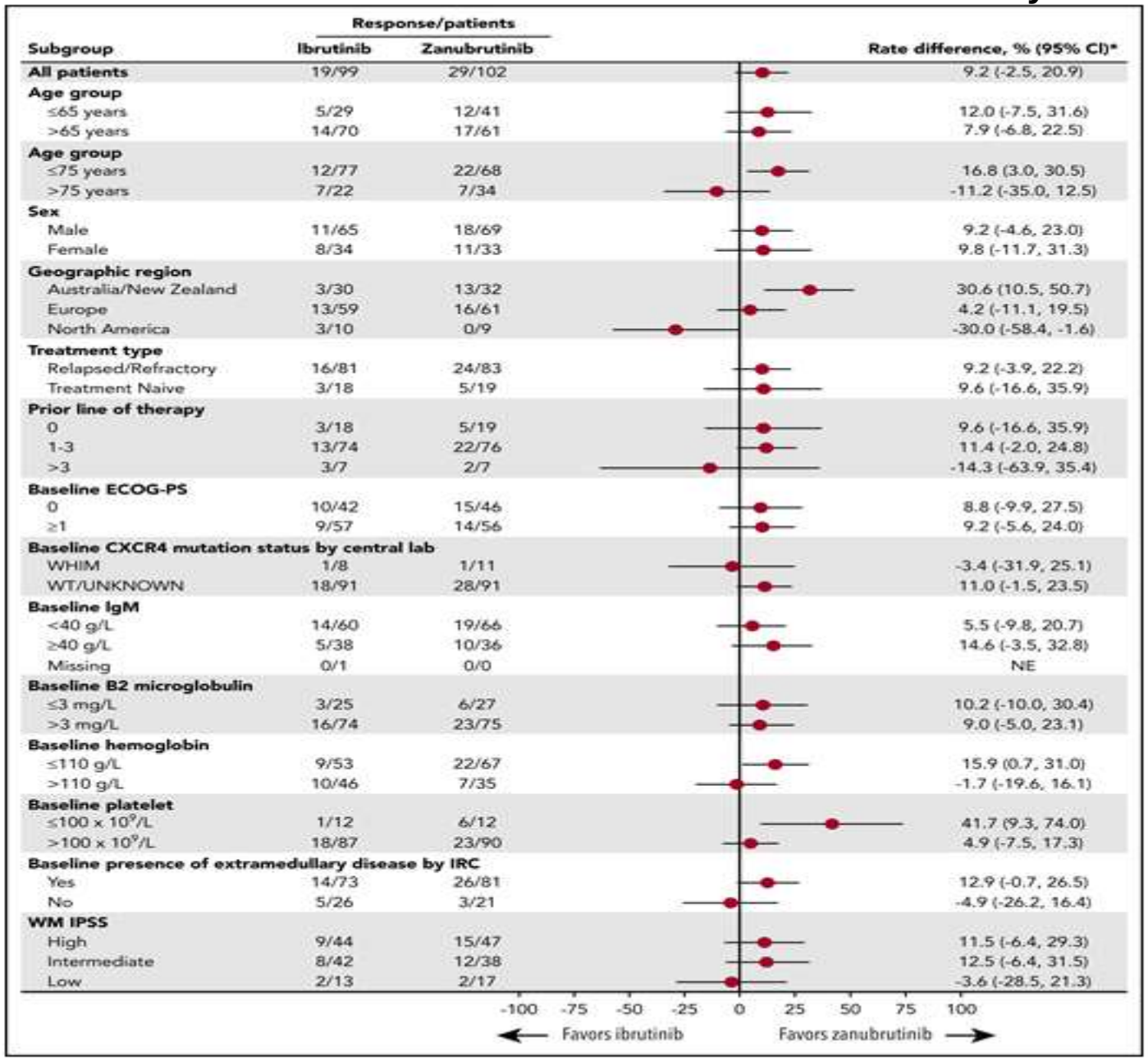
A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study



Subgroup	Response/patients: Ibrutinib	Response/patients: Zanubrutinib	Rate difference, % (95% CI)*
All patients	19/99	29/102	9.2 (-2.5, 20.9)
Age group			
≤65 years	5/29	12/41	12.0 (-7.5, 31.6)
>65 years	14/70	17/61	7.9 (-6.8, 22.5)
Age group			
≤75 years	12/77	22/68	16.8 (3.0, 30.5)
>75 years	7/22	7/34	-11.2 (-35.0, 12.5)
Sex			
Male	11/65	18/69	9.2 (-4.6, 23.0)
Female	8/34	11/33	9.8 (-11.7, 31.3)
Geographic region			
Australia/New Zealand	3/30	13/32	30.6 (10.5, 50.7)
Europe	13/59	16/61	4.2 (-11.1, 19.5)
North America	3/10	0/9	-30.0 (-58.4, -1.6)
Treatment type			
Relapsed/Refractory	16/81	24/83	9.2 (-3.9, 22.2)
Treatment Naive	3/18	5/19	9.6 (-16.6, 35.9)
Prior line of therapy			
0	3/18	5/19	9.6 (-16.6, 35.9)
1-3	13/74	22/76	11.4 (-2.0, 24.8)
>3	3/7	2/7	-14.3 (-63.9, 35.4)
Baseline ECOG-PS			
0	10/42	15/46	8.8 (-9.9, 27.5)
≥1	9/57	14/56	9.2 (-5.6, 24.0)
Baseline CXCR4 mutation status by central lab			
WHIM	1/8	1/11	-3.4 (-31.9, 25.1)
WT/UNKNOWN	18/91	28/91	11.0 (-1.5, 23.5)
Baseline IgM			
<40 g/L	14/60	19/66	5.5 (-9.8, 20.7)
≥40 g/L	5/38	10/36	14.6 (-3.5, 32.8)
Missing	0/1	0/0	NE
Baseline B2 microglobulin			
≤3 mg/L	3/25	6/27	10.2 (-10.0, 30.4)
>3 mg/L	16/74	23/75	9.0 (-5.0, 23.1)
Baseline hemoglobin			
≤110 g/L	9/53	22/67	15.9 (0.7, 31.0)
>110 g/L	10/46	7/35	-1.7 (-19.6, 16.1)
Baseline platelet			
≤100 x 10^9/L	1/12	6/12	41.7 (9.3, 74.0)
>100 x 10^9/L	18/87	23/90	4.9 (-7.5, 17.3)
Baseline presence of extramedullary disease by IRC			
Yes	14/73	26/81	12.9 (-0.7, 26.5)
No	5/26	3/21	-4.9 (-26.2, 16.4)
WM IPSS			
High	9/44	15/47	11.5 (-6.4, 29.3)
Intermediate	8/42	12/38	12.5 (-6.4, 31.5)
Low	2/13	2/17	-3.6 (-28.5, 21.3)

A higher rate of CR/VGPR was observed for zanubrutinib vs ibrutinib (28% vs 19%) (NS)

Zanubrutinib was associated with a trends toward better response quality and less toxicity

CR: 0
VGPR: 19% vs 28%, p=.09
MRR 78% vs 77%
DOR and PFS NR
PFS 18 m: 84 vs 85%

Tam CS et al, Blood, 2020;136

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Zanubrutinib for the treatment **of MYD88 wild-type Waldenström macroglobulinemia**: a substudy of the phase 3 ASPEN trial

Table 2. IRC-assessed efficacy outcomes per modified IWWM-6 consensus criteria

	Treatment-naïve (n = 5)	Relapsed/refractory (n = 21)	Overall (N = 26)
Best overall response, n (%)			
VGPR	1 (20)	6 (29)	7 (27)
PR	1 (20)	5 (24)	6 (23)
MR	2 (40)	6 (29)	8 (31)
SD	1 (20)	3 (14)	4 (15)
PD	0	1 (5)	1 (4)
Response rates, % (95% CI)*			
VGPR or CR rate	20 (1, 72)	29 (11, 52)	27 (12, 48)
MRR	40 (5, 85)	52 (30, 74)	50 (30, 70)
ORR	80 (28, 100)	81 (58, 95)	81 (61, 93)
Duration of overall response, % (95% CI)†			
6-mo event-free rate	100	88 (60, 97)	90 (66, 98)
12-mo event-free rate	50 (6, 85)	74 (44, 89)	68 (42, 84)
Duration of CR/VGPR, % (95% CI)†			
6-mo event-free rate	100	100	100
12-mo event-free rate	0	100	75 (13, 96)
Duration of major response, % (95% CI)†			
6-mo event-free rate	100	89 (43, 98)	91 (51, 99)
12-mo event-free rate	0	78 (37, 94)	62 (28, 84)
Progression-free survival, % (95% CI)†			
12-mo event-free rate	80 (20, 97)	71 (46, 86)	72 (51, 86)
18-mo event-free rate	60 (13, 88)	71 (46, 86)	68 (46, 83)
Overall survival, % (95% CI)†			
12-mo event-free rate	100	95 (71, 99)	96 (76, 99)
18-mo event-free rate	80 (20, 97)	90 (65, 97)	88 (67, 96)

Percentages are based on N, the number of randomized patients.
CI, confidence interval; CR, complete response; IRC, independent review committee; MR, minimal response; MRR, major response rate; ORR, overall response rate; PD progressive disease; PR, partial response; R/R, relapsed or refractory; SD, stable disease; VGPR, very good partial response.
*95% CIs estimated using the Clopper-Pearson method.

Follow-up: 17,9 m

6 pts progression
(no transformation Dis)

PFS estimated 18 m 68%
OS estimated 18 m: 88%

No CR

CXCR4 mut

Patients with *MYD88*^{WT} WM treated with zanubrutinib achieved a ORR 80%, a 50% major response rate (including 27% VGPRs) and 18-month PFS rate of 68%.

Dimopoulos MA *et al*, Blood Adv, 2020;4

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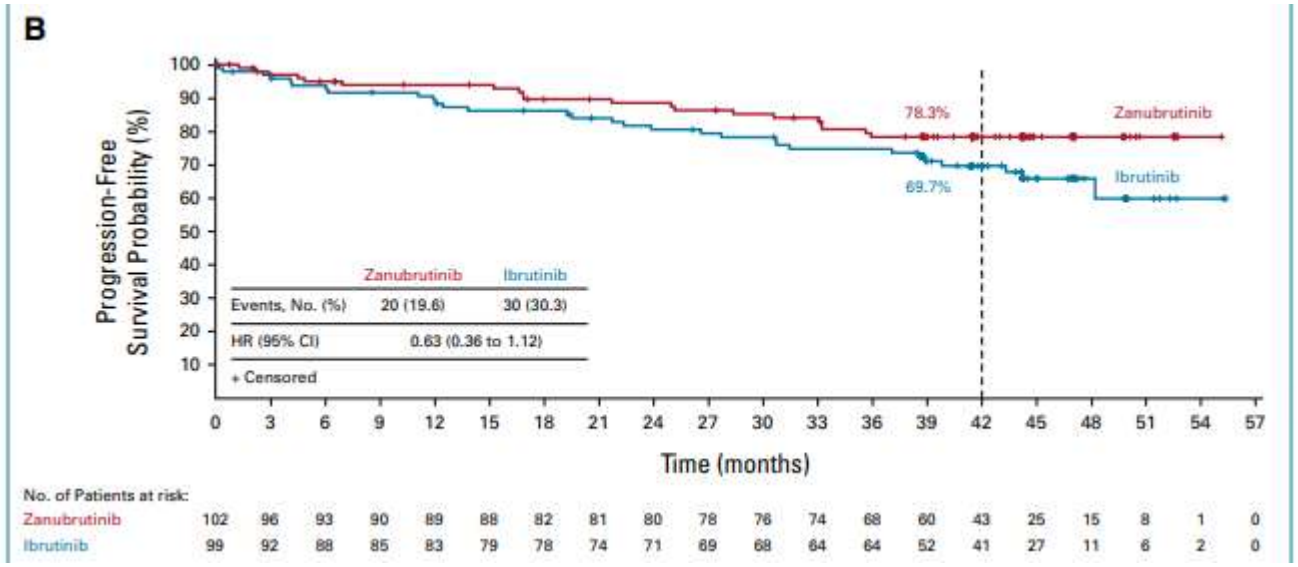
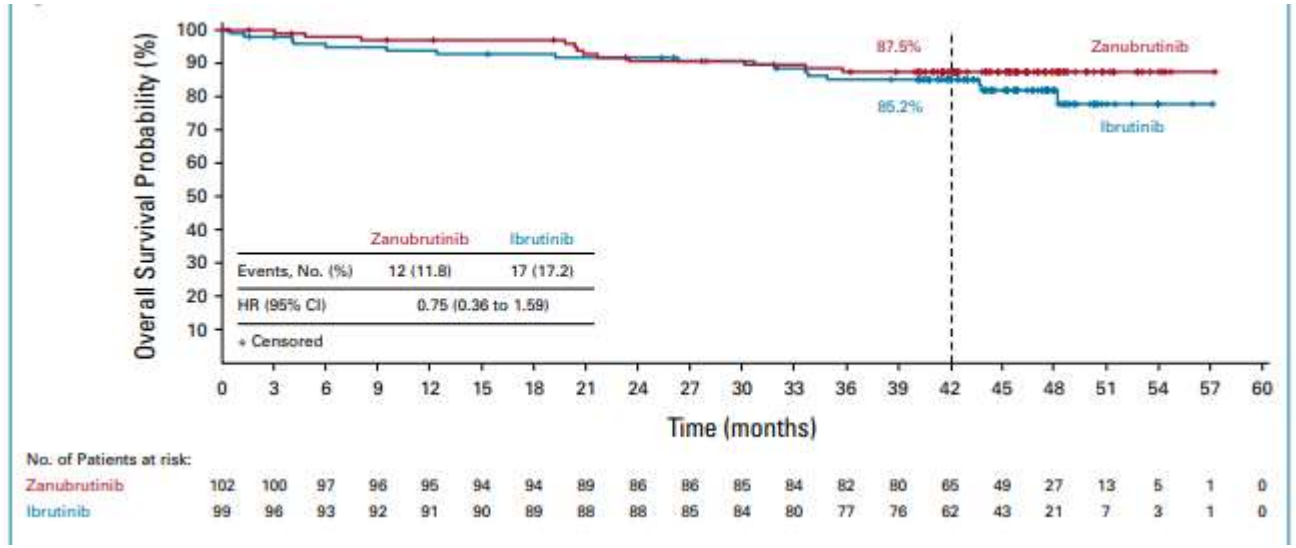
Final study aspen





Final study: 44,4 months median follow up

CR+VGPR rates 36,3% vs 25,3%

Median time to CR+VGPR was 6,7 months vs 16,6 months

Median PFS and OS were not reached

Dimopoulos Ma et al. J Clin Oncol. 2023 Jul 21

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Consensus panel from the 11th IWWM on management of symptomatic, treatment-naïve patients

"based on individual patients characteristics, genomics, comorbidities and disease dynamics"

1- **Asymptomatic WM**:
- W & W
- High risk calculator
- High risk IPSSWM

} No criteria to start therapy

2- **Symptomatic WM**:

- Fixed duration chemoimmunotherapy
- indefinite duration oral therapies

Buske Ch *et al*. Sem Hematol, 2023;60

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Consensus panel from the 11th IWWM on management of symptomatic, treatment-naïve patients

Symptomatic WM:

1- **Fixed duration chemoimmunotherapy**

-**R-bendamustine** (SOC)	bulky disease trend to longer PFS and TTNT 90 mg/m2 x 6 cycles
- R-CD	gradual progression unfit lower tumor burden
- PI-based therapy	AL light chain deposition disease renal compromise

Buske Ch *et al*. Sem Hematol, 2023;60

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Consensus panel from the 11th IWWM on management of symptomatic, treatment-naïve patients

Symptomatic WM:

2- **Indefinite duration oral therapies : cBTKi**

comorbidities
frailty
young patients?
MYD 88 and *CXCR4* mutational status?

Zanubrutinib vs ibrutinib

Trend of deeper , earlier and durable responses in *MYD88* ^{mut}, *MYD88* ^{wt} and *CXCR4* mut

Buske Ch *et al*. Sem Hematol, 2023;60

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Consensus panel from the 11th IWWM on management of symptomatic, treatment-naïve patients
Other conditions

Bing Neel Syndrome: - Ibrutinib
- MTX, cytarabine, Bendamustine, fludarabine in R/R patients
- Zanubrutinib ?

Distal acquired demyelinating sensory neuropathy: Rituximab +/- chemotherapy

Hyperviscosity Syndrome: Plasmapheresis + systemic treatment

AL amyloidosis: PI-based regimens, R-bendamustine

Cryoglobulins, cold agglutinins: CIT, PI-based treatment, cBTK i

Castillo JJ, Treon SP. BJH , 2019; 187
Buske Ch *et al*. Sem Hematol, 2023;60
Wong J *et al*. Hemasphere,2018; 2

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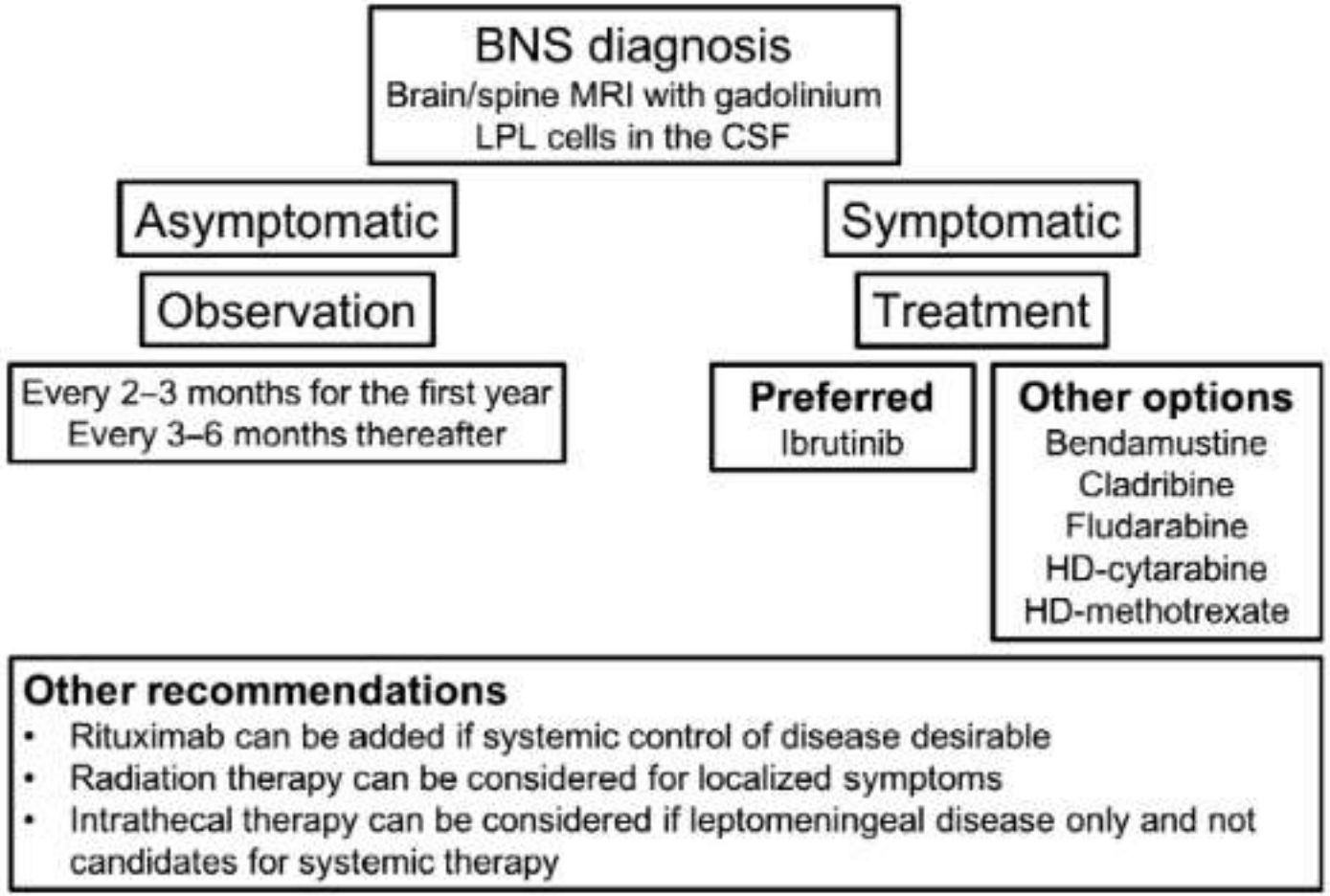

Fig 2. Recommended treatment algorithm for patients with Bing–Neel syndrome. BNS, Bing–Neel syndrome; CSF, cerebrospinal fluid; HD, high-dose; LPL, lymphoplasmacytic lymphoma; MRI, magnetic resonance imaging.

Castillo JJ, Treon SP. BJH , 2019; 187

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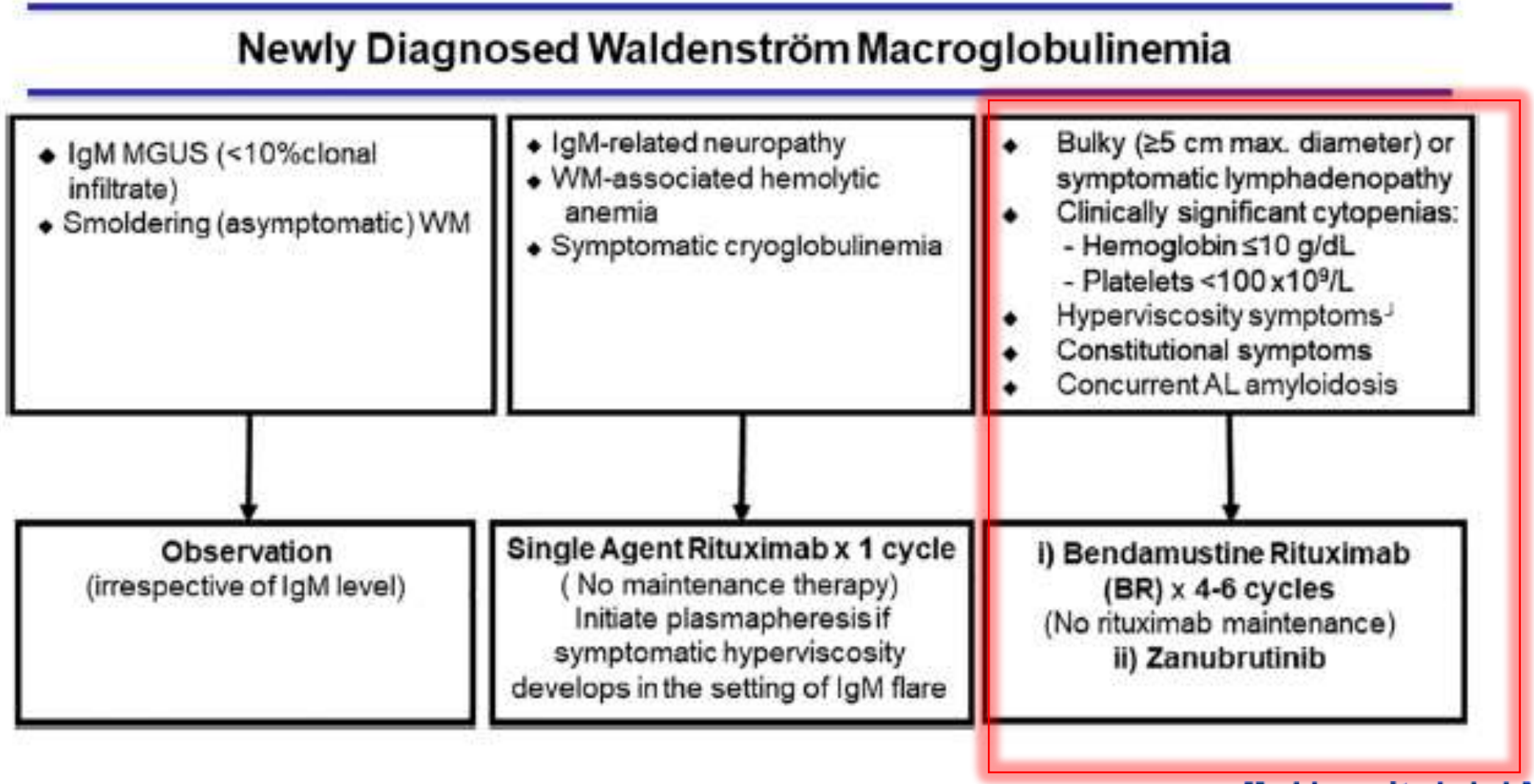
Mayo clinic consensus for newly diagnosed Waldenström macroglobulinemia



Adapted from Gertz M. Am J Hematol 2023; 98

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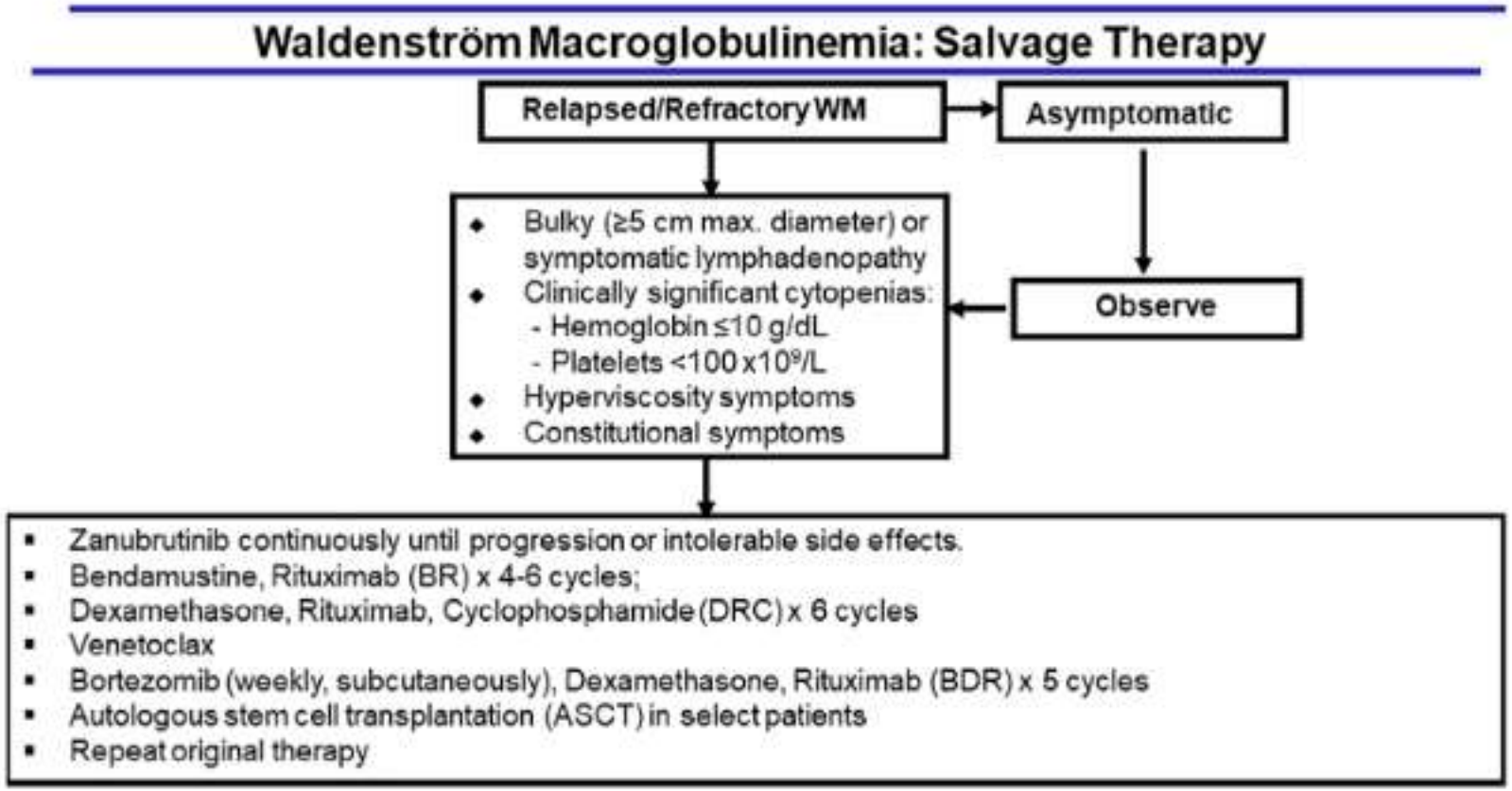
Mayo clinic consensus



Non-covalent BTK inhibitors

Pirtobrutinib

- High response rates (MRR: 6S%; CR+VGPR: 24%) in BRUIN (n = 66 RRWM who had discontinued covalent BTKi due to relapse [67%] or intolerance [33%])
- Shows efficacy in $MYD88^{WT}$, BTK^{C481S}, BTK^{C481R} mutated patients
- Limited follow up
- Not currently approved for WM
- Most frequent Grade >3 TEAE was neutropenia (20%)
- Superiority over covalent BTKi remains to be established

Adapted from Gertz M. Am J Hematol 2023; 98

Palomba ML et al. Blood 2022; 140

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Other targeted therapies: potential benefits and drawbacks.

	Potential benefits	Potential drawbacks	Unknowns/Caveats
BCL-2 inhibitors			
Venetoclax	• Phase 2 study with 24-month fixed-duration therapy: ORR 84% MRR 81% VGPR 19% (n = 32, 16 previous BTKI, all $MYD88^{MUT}$, 17 $CXCR4^{MUT}$)	• No CRs • Significant progression within 6 months of completing 24 months- suggesting continuous therapy required • Phase 2 study of fixed-duration venetoclax with ibrutinib: (n = 45 TN patients) closed prematurely due to unexpected fatal ventricular tachycardias	• Potential for combination of (other) BCL-2 inhibitors with (other) BTKi: studies on hold NCCN-recommended regimen, previously treated
Proteasome inhibitors			
Bortezomib	• ORR 80%, PR 60% using monotherapy (RRWM) • CyBorD regimen (n = 11 RRWM): ORR 93%, MRR 53% • Real world data of Bortezomib-containing therapy (n = 32 RRWM): ORR 88%, median TTNT 66 months. Neuropathy Grade 1-2 in 24%; no treatment cessation due to AEs. Major responses comparable in BTKi-failures vs no BTKi	• Monotherapy study: Treatment emergent neuropathy (30%) (grade 2: n = l, grade 3: n = 2] • CyBordD study: Grade 3-4toxicities requiring dose changes/delajys included neuropathy (26%), cytopenia (20%), and bacteraemia (7%).	• Unclear where bortezomib fits in
Carfilzomib	• CaRD is a study in TN patients (n-33): ORR 87%, MRR 68%	• Limited data outside of trials	• Potential for cardiopulmonary toxicity
Ixazomib	• Fixed-duration Ixazomib + SC flat dose Rituximab + Dexamethasone (n = 59 RRWM): ORR 71%, VGPR 14%, PR 37% • Phase 2 study of combination of ibrutinib with ixazomib (n = 21 TN and RRWM): VGPR 24% PR 52%	• Hovon study: hematological toxicity (n = 6), infusion-related reactions to rituximab (n = 2) neurotoxicity (n = 5) and other toxicities (n = 21) • The safety analysis of the combination study: anaemia (81%), fatigue (76%), nausea (67%) and thrombocytopenia (52%) were the most common AEs.	

Castillo JJ et al. Blood advances 2020; 4
Castillo JJ et al. J Clin Oncol, 2021; 40
D'Sa D et al, Sem Hematol , 2023; 60

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Gosta Waldenström
Stockholm, 1906-19

Conclusions

- Immunochemotherapy remains the standard of treatment in most patients with WM

- cBTKi are effective in first line and also in subsequent lines

- CXCR4 mutated patients show a slower response to cBTKi.
  MYD88 and *CXCR4* mutational status should be performed in patients starting treatment

- Management of IgM- related disorders could be the only reason to treat patients

- New targeted therapies open new paths for refractory patients


Grup de Recerca clínica aplicada a Malalties Hematològiques
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